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Adjuvant denosumab treatment in patients with resectable high-risk giant cell tumor of bone

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ABSTRACT

Aims: Giant cell tumor of bone (GCTB) is an uncommon, benign, but aggressive osteolytic skeletal neoplasm of young adults. Although denosumab is frequently used in neoadjuvant treatment and metastatic unresectable disease in these patients, its role in adjuvant therapy is unclear. In this study, we evaluated the efficacy and safety of denosumab as an adjuvant therapy in patients with resectable high-risk GCTB.

Methods: Patients with resectable high-risk GCTB over the age of 16 who received postoperative denosumab between January 2013 and September 2022 were included. Demographic and clinical characteristics of the patients, tumor localization, prior treatments, response to denosumab treatment, and adverse effects of the drug were analyzed retrospectively.

Results: A total of 18 patients (10 women) with a median age of 23 (16-45) years were recruited. The median follow-up time was 7.1 (4.2-8.7) years and the median denosumab treatment duration was 12 (12-90) months. One (6%) patient experienced a partial response, and 17 (94%) patients had stable disease. Grade 1 or 2 hypophosphatemia was the most frequent adverse effect (16.7%, n=3). No patients stopped therapy due to side effects, and no grade 3 or 4 incident were observed.

Conclusion: Postoperative denosumab may also be useful in the adjuvant treatment of patients with high-risk resectable GCTB.

Keywords: Giant cell tumor of bone, denosumab, adjuvant drug therapy

INTRODUCTION

Giant cell tumor of bone (GCTB) is a relatively rare, benign, but locally aggressive osteolytic skeletal neoplasm affecting young adults.[1,2] GCTB accounts for 3 to 5% of all primary bone tumors.[3,4] Although considered a benign tumor, GCTB represents a spectrum of neoplasms with unpredictable behavior based on clinical, radiological, and histologic characteristics. GCTB can erode bones and spread into the surrounding soft tissue, producing discomfort, significant morbidity, and occasionally metastasis. Curative surgery, either curettage or resection, is the standard treatment; nevertheless, some areas may not be amenable to resection, and local recurrence can occur at any site.[5] Even after curettage, GCTB tends to recur locally. Furthermore, distant metastases, which most frequently spread to the lungs, occur in about 2-3% of cases.[6,7]

GCTB is composed of osteoclast-like giant cells and mononuclear stromal cells.[8] Although it is assumed that the neoplastic component is generated from the stromal compartment, the precise cellular origin remains unknown. Because of their proliferative abilities, spindle-like stromal cells constitute the neoplastic component of GCTB.[8] Besides these, receptor activator of nuclear factor kappa B ligand (RANKL) appears to have a crucial role in the pathophysiology of GCTB.[9,10] Stromal cells express RANKL, while giant cells express RANK, and elevated levels of RANKL lead to more bone lysis and destruction.[11,12] However, the fundamental cause of the elevated RANKL expression by stromal cells remained unclear. Nevertheless, the most persuasive evidence for the role of RANKL signalling in the pathophysiology of GCTB comes from numerous phase II trials with denosumab, which shown that blocking RANKL signalling is a potent and effective therapy in this disease.[13-16] Denosumab, a RANKL-inhibiting human monoclonal antibody, is approved for the treatment of adults and skeletally mature adolescents with metastatic

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or unresectable GCTB or when surgical resection is anticipated to result in significant morbidity.[17] However, data on the use of denosumab in the adjuvant setting are very limited.[18,19] Therefore, we aimed to evaluate the efficacy and safety of postoperative denosumab in patients with resectable high-risk primary GCTB in real-life.

METHODS

Ethics

This research was conducted in compliance with the Helsinki Declaration of 1964 and its subsequent amendments. All participants were informed in detail about the research and written informed consent was obtained from all of the subjects. The study was authorized by Hacettepe University Non-interventional Clinical Researches Ethics Committee (Date: 10.01.2023, Decision No: GO 12/1326).

Patients

We retrospectively evaluated patients with histologically confirmed localized GCTB over the age of 16 years who received postoperative denosumab between January 2013 and September 2022. Demographic and clinical characteristics of the patients, tumor localization, previous treatments, response to therapy, and drug-related side effects were recorded. R0 resection was not achieved in any of the patients who underwent wide excision without surgical adjuvants. Postoperative residual tissues were diagnosed with magnetic resonance imaging (MRI). Before the treatment, all patients were evaluated by a multidisciplinary team. Denosumab (120 mg) was injected subcutaneously every 28 days, with additional injections on days 8 and 15 in the first month. Calcium (600 mg/day) and vitamin D (400 IU/day) supplements were also given to all patients. Following denosumab therapy, patients were followed using MRI or computed tomography scans of the area of interest, as appropriate. Response rates were assessed according to "Response Evaluation Criteria In Solid Tumors" (RECIST) 1.1. The radiographic findings were classified into four groups: complete response, partial response, stable disease, and progressive disease. The "Common Terminology Criteria for Adverse Events" (CTCAE; version 3.0) were used to evaluate adverse events and laboratory abnormalities.

Statistical Analysis

Statistical analyzes were performed using SPSS version 28 software. Due to the small number of participants, only descriptive statistics were presented with frequency (%) and median (min-max).

RESULTS

A total of 18 patients (10 women and 8 men) with a median age of 23 (16-45) years were recruited. The median age at diagnosis was 15.5 (4-39) years. The Eastern Cooperative Oncology Group Performance Status was grade 1 in 12 (66.6%) and grade 2 in 6 (33.3%) patients. The primary lesions were located in lower limb (33.3%, n=6), vertebrae (27.8%, n=5), pelvic bone (16.7%, n=3), skull (11.1%, n=2), and upper limb (11.1%, n=2). Ten (55.6%) patients had Campanacci class 2 and 8 (44.4%) had class 3 tumors. Previous treatments were radiation therapy (22.2%, n=4) and arterial embolization (5.5%, n=1), as shown in Table.

Table. Baseline characteristics of patients.

Characteristics	Frequency (%), n=18
Age, median (min-max), years	23 (16-45)
Age at diagnosis, median (min-max), years	15.5 (4-39)
Sex	
Women	10 (55.6)
Men	8 (44.4)
ECOG PS	
Grade 1	12 (66.6)
Grade 2	6 (33.3)
Tumor location	
Lower limb	6 (33.3)
Vertebrae	5 (27.8)
Pelvic bone	3 (16.7)
Skull	2 (11.1)
Upper limb	2 (11.1)
Campanacci classification	
Stage I	0 (0)
Stage II	10 (55.6)
Stage III	8 (44.4)
Previous therapies	
Radiation therapy	4 (22.2)
Arterial embolization	1 (5.5)

min: Minimum, max: Maximum, ECOG PS: The Eastern Cooperative Oncology Group Performance Status

The median follow-up time was 7.1 (4.2-8.7) years and the median denosumab treatment duration was 12 (12-90) months. While 17 (94%) patients had stable disease, partial response was obtained in 1 (6%) patient (Figure 1). No complete response or progression was observed.

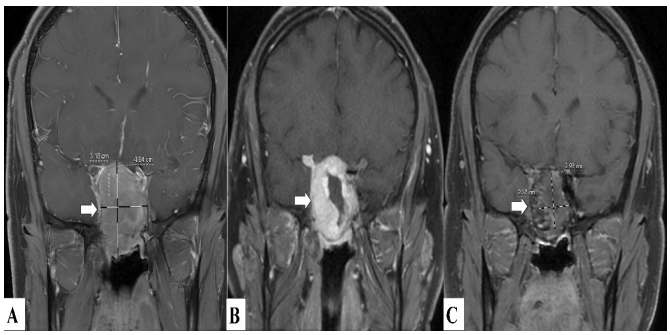

Figure 1. Brain magnetic resonance imaging-T1 series. a) A 4.64x3.18 cm solid lesion with irregular borders and lobulated contours, located in the midline clival, compressing the chiasm and prechiasmatic segments of the optic nerves. b) One month after transsphenoidal partial excision surgery. c) Significant reduction in lesion size (2.93x2.33 cm) after seven months of adjuvant denosumab.

Denosumab was generally well tolerated and no grade 3 or 4 side effects were encountered. Grade 1 or 2 side effects consisted of hypophosphatemia (16.7%, n=3) and

hypercalcemia (11.1%, n=2). No patient had discontinued therapy due to side effects.

DISCUSSION

This study represents the results of adjuvant denosumab therapy in patients with high-risk resectable GCTB. Our findings demonstrate that denosumab is effective and safe option in this group. Denosumab's therapeutic effect is related to its activities against RANKL.[20,21] GCTB is distinguished by stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK. Denosumab works by binding to RANKL, which results in a significant reduction or elimination of osteoclast-like giant cells. As a consequence, osteolysis is stopped, and the proliferative stroma of the tumor is replaced by non-proliferative new bone that is differentiated and densely woven.[12]

The first studies of denosumab in GCTB revealed that administration of denosumab resulted in a significant reduction in the number of giant tumor cells and histological differentiation of highly proliferative stromal tumor cells into non-proliferative osteoid bone matrix, woven bone, or mature bone.[12,13] After the discovery of the antitumor effect of denosumab, many clinical studies were conducted in patients with GCTB. Especially, denosumab was approved in the neoadjuvant setting based on many non-randomized phase II trials and observational studies. When taken prior to extensive en-bloc resection, it reduces tumor burden and local recurrence rates while increasing surgical downstaging rates.[16,22,23]

Denosumab is also used chronically in the metastatic disease and unresectable tumors. The length of therapy, negative consequences from prolonged use, and the possibility of treatment interruption, however, are still open issues.[24] On the other hand, data on the use of denosumab in adjuvant setting are very limited. There is only one retrospective observational study in the literature on this subject. In that study, Errani et al.[19] compared 222 GCTB patients who underwent curettage alone with 25 patients who received curettage plus adjuvant denosumab. They observed local recurrence rate 16% in the first group and 60% in the denosumab group ($p<0.001$). In addition, denosumab use was shown as an independent poor risk factor for relapse-free survival in the multiple regression model (HR: 4.78, 95% CI: 2.45-9.35). In our study, on the contrary, stable disease was observed in 94% of patients and partial response was achieved in 6% of patients during a similar follow-up period of approximately 7 years. Significant differences between that research and ours include the inclusion of only extremity tumors and the use of adjuvant phenol applications as well as analysis with historical controls. In the group of patients with a high risk of recurrence, it needs to be studied whether adding denosumab in the adjuvant setting is beneficial. The duration of denosumab therapy is also controversial. According to our data, denosumab could be used as adjuvant therapy in patients with postoperative residual disease. We administered it as an adjuvant for at least a year. Additionally, in a patient with GCBT in the sacral region, the adjuvant denosumab was used for 90 months, considering the postoperative residual disease and the risk of serious morbidity in the occasion of recurrence (Figure 2). Since data on adjuvant denosumab therapy and treatment duration are limited, adjuvant therapy could be given on a patient-by-patient basis. Prospective studies are needed to clarify which patient group would benefit from adjuvant therapy more.

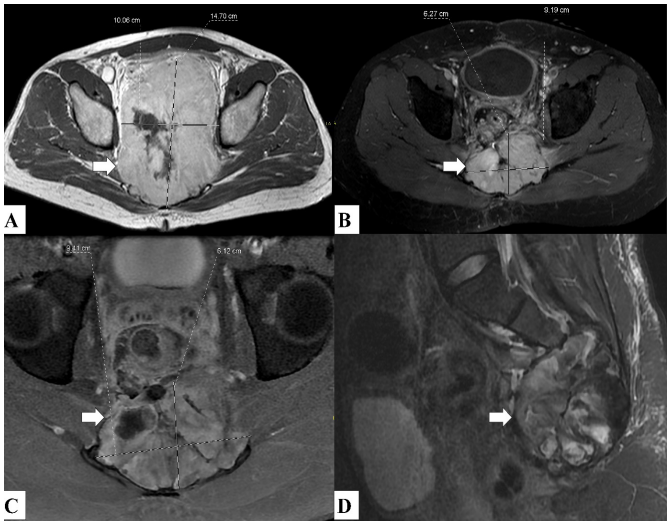

Figure 2. Pelvic magnetic resonance imaging-T1 series. a) A 14.7x10.06 cm giant cell tumor of bone involving the sacral vertebrae, extending to the presacral region and compressing the rectum. b) Postoperative first month appearance of the mass. c-d) Stable disease after 90 months of adjuvant denosumab treatment.

Treatment with denosumab is generally well tolerated, with a low frequency of significant adverse effects. Hypophosphatemia, which occurred in 5% of patients, was one of the most common side effects of denosumab in one clinical trial.[25] In our study, 3 (16.7%) patients had hypophosphatemia and all of them were easily managed with phosphorus replacement. In a study of 97 patients, Palmerini et al.[25] observed that jaw necrosis was the most common complication (11%), and also atypical femoral fracture (4%) was another serious adverse effect. In another research of 138 GCTB patients treated with denosumab, one patient (0.7%) had jaw osteonecrosis.[22] Although different rates of side effects were reported in various studies, we did not observe serious side effects, perhaps due to the small number of patients in our study. However, several studies, including our data, support that denosumab is safe and well tolerated in GCBT patients.

Limitations

Our study has some limitations such as retrospective design and the relatively small sample size. Additionally, factors influencing survival and treatment response could not be investigated because of the small number of patients and the low incidence of events.

CONCLUSION

Denosumab therapy in GCTB is associated with a high tumor control rate with a favorable profile. It is authorized for use in metastatic, irresectable cancer and neoadjuvant settings. Our study supports that denosumab may also be useful in the adjuvant treatment of high-risk resectable patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Hacettepe University Non-interventional Clinical Researches Ethics Committee (Date: 10.01.2023, Decision No: GO 12/1326).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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